Study update of the oral CDK9 inhibitor KB-0742 in relapsed or refractory transcriptionally addicted advanced solid tumors

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Poster Board #247

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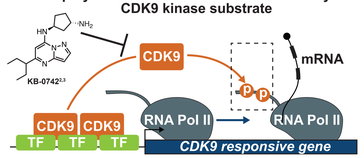
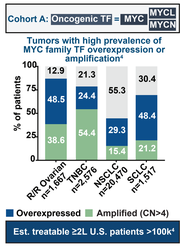
KB-0742 is a highly selective, orally bioavailable inhibitor of CDK9, a critical cofactor of oncogenic transcription factor activity

- Cyclin-dependent kinase 9 (CDK9) is a hub for transcriptional control that interacts with many oncogenic transcription factors (TFs), making it a promising therapeutic target in transcriptionally addicted tumors.
- Both MYC deregulated solid tumors (Cohort A) and sarcomas with TF fusions (Cohort B) exhibit high dependency on cyclin-dependent kinase 9 (CDK9) activity.
- KB-0742 is a potent, selective, and orally bioavailable inhibitor of CDK9 with a 24-hour plasma half-life enabling intermittent dosing. KB-0742 is being evaluated in an ongoing Phase 1/2 study in advanced solid tumors (NCT04718675).
- Objective single agent anti-tumor activity in myxoid liposarcomas with TF fusions has been demonstrated[1].

CDK9 is a kinase that is recruited to the genome by transcription factors and drives transcription elongation

Phosphorylated serine 2 (pSER2) of the RNA polymerase II C-terminal domain is a key CDK9 kinase substrate





Est. treatable ≥2L U.S. patients >100k[4]

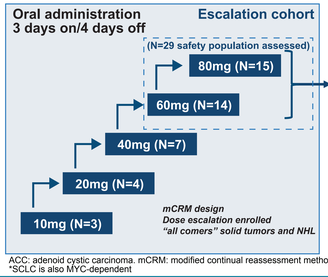
Cohort B: Oncogenic TF = TF#1 TF#2 Fusion; Oncogenic TF = Lineage Specific TF		
Example tumor type	**TF#1**	**TF#2**
Ewing sarcoma	EWSR1	FLI1
	FUS	ERG
Myxoid liposarcoma	DDIT3	FUS
Adenoid cystic carcinoma	MYB	NFIB
Alveolar rhabdomyosarcoma	PAX3	FOXO1
	PAX7	FOXO1

Example tumor type	Example lineage TF
Small cell lung cancer*	NEUROD1
	ASCL1
*SCLC is MYC deregulated and also addicted to lineage specific TFs (Cohort B)	POU2F3
	YAP1

Est. Drug Treatable U.S. Patients >50k[4,5,6,7]

KB-0742-1001 study current status: dose escalation and expansion on 3 days on/4 days off schedule with data presentation on 60mg and 80mg cohorts

Phase 1/2, first-in-human, open-label dose escalation and expansion study of KB-0742 in patients with relapsed or refractory solid tumors (NCT04718675)



Expansion cohorts at 60mg and 80mg at 3 days on/4 days off (N=74 safety population assessed)

Cohort A:
MYC-dependent solid tumors ovarian, TNBC, NSCLC
N=11 at 60mg
N=5 at 80mg

Cohort B:
Other transcriptionally addicted tumors SCLC*, TF fusion-driven cancers (e.g., sarcomas, ACC)
N=57 at 60mg
N=1 at 80mg

Patient Characteristic	60mg (N=82)	80mg (N=21)	60mg and 80mg (N=103)
Median age, years (range)	59 (17-84)	64 (23-76)	60.0 (17-84)
Female, n (%)	36 (43.9)	13 (61.9)	49 (47.6)
Number of prior systemic anticancer regimens, median (range)	2.5 (0-9)	4 (0-9)	3 (0-9)

Goals	To determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and evaluate the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of KB-0742 in patients with relapsed/refractory (R/R) solid tumors
Eligibility	• Any R/R solid tumor • Age > 12 yrs (US), acceptable organ function and ECOG PS <2 • Cohort A tumor types: ovarian cancer, TNBC, NSCLC; • Cohort B tumor types: SCLC, Sarcoma with TF fusion Chordoma, NUT carcinoma, or adenoid cystic carcinoma
Endpoints	The primary endpoint includes a descriptive safety analysis of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), and laboratory assessments

ACC: adenoid cystic carcinoma. mCRM: modified continual reassessment method; NHL: Non-Hodgkin lymphoma; NSCLC: non-small cell lung cancer. SCLC: small cell lung cancer. TF: transcription factor. TNBC: triple negative breast cancer.
*SCLC is also MYC-dependent

In 103 patients treated in the 60mg and 80mg cohorts, KB-0742 demonstrated manageable safety and tolerability with no observed Grade 3/4 neutropenia

KB-0742 TEAEs occurring in ≥ 15% of patients for 60mg and 80mg dose levels

Event	60mg (N=82)		80mg (N=21)		60mg and 80mg (N=103)	
	All grades	Grade 3	All grade	Grade 3	All Grade	Grade 3
Any TEAE n(%)	81 (98.8)	31 (37.8)	21 (100)	9 (42.9)	102 (99.0)	40 (38.8)
Nausea	57 (69.5)	2 (2.4)	15 (71.4)	0	72 (69.9)	2 (1.9)
Vomiting	45 (54.9)	2 (2.4)	9 (42.9)	0	54 (52.4)	2 (1.9)
Fatigue	24 (29.3)	0	6 (28.6)	0	30 (29.1)	0
Constipation	21 (25.6)	0	3 (14.3)	0	24 (23.3)	0
Anaemia	18 (22.0)	3 (3.7)	4 (19.0)	1 (4.8)	22 (21.4)	4 (3.9)
Diarrhoea*	16 (19.5)	1 (1.2)	5 (23.8)	0	21 (20.4)	1 (1.0)
Hyponatraemia	14 (17.1)	1 (1.2)	5 (23.8)	1 (4.8)	19 (18.4)	2 (1.9)

*TEAE Diarrhoea Grade 4, reported in one patient, administered KB-0742 80 mg 3 days on/4 days off
Note: TEAE = Treatment Emergent Adverse Event; MedDRA v23.1

Hematologic Abnormalities

Event	60mg (N=82)		80mg (N=21)		60mg and 80mg (N=103)	
Hematologic TEAE* n(%)	All grade	Grade 3**	All grade	Grade 3**	All grade	Grade 3**
Anaemia	18 (22.0)	3 (3.7)	4 (19.0)	1 (4.8)	22 (21.4)	4 (3.9)
Lymphopenia	12 (14.6)	5 (6.1)	1 (4.8)	0	13 (12.6)	5 (4.9)
Neutropenia	2 (2.4)	0	0	0	2 (1.9)	0
Thrombocytopenia	5 (6.1)	1 (1.2)	2 (9.5)	0	7 (6.8)	1 (1.0)

*Based on NCI-CTCAE grading
*No grade 4 or 5 anaemia, lymphopenia, neutropenia, or thrombocytopenia events were reported.

Treatment-emergent central nervous system and psychiatric events

Event	60mg (N=82)		80mg (N=21)		60mg and 80mg (N=103)	
TEAE n(%)	All grade	Grade 3*	All grade	Grade 3*	All grade	Grade 3*
Headache	14 (17.1)	1 (1.2)	1 (4.8)	1 (4.8)	15 (14.6)	2 (1.9)
Dizziness	10 (12.2)	1 (1.2)	3 (14.3)	0	13 (12.6)	1 (1.0)
Confusional state	4 (4.9)	0	5 (23.8)	0	9 (8.7)	0
Hallucination	3 (3.7)	0	3 (14.3)	0	6 (5.8)	0
Dyskinesia	2 (2.4)	0	3 (14.3)	0	5 (4.9)	0
Insomnia	5 (6.1)	0	0	0	5 (4.9)	0
Tremor	4 (4.9)	0	1 (4.8)	0	5 (4.9)	0
Memory impairment	4 (4.9)	1 (1.2)	0	0	4 (3.9)	1 (1.0)
Encephalopathy	3 (3.7)	2 (2.4)	0	0	3 (2.9)	2 (2.0)
Seizure	2 (2.4)	2 (2.4)	1 (4.8)	1 (4.8)	3 (2.9)	3 (2.9)
Delirium	1 (1.2)	0	1 (4.8)	0	2 (1.9)	0
Mental status changes	2 (2.4)	0	0	0	2 (1.9)	0
Cognitive disorder	1 (1.2)	0	0	0	1 (1.0)	0
Myoclonus	1 (1.2)	0	0	0	1 (1.0)	0

*No Grade 4 of 5 events were reported

Patient disposition and discontinuation summary

Reason for withdrawal from study drug	60mg (N=82)	80mg (N=22)	60mg and 80mg (N=104)
n(%)			
Disease progression	50 (61.0)	10 (45.5)	60 (57.7)
Adverse event	7 (8.5)	3 (13.6)	10 (9.6)
Withdrawal consent by the patient	15 (18.3)	4 (18.2)	19 (18.3)
Lost to follow-up	1 (1.2)	1 (4.5)	2 (1.9)
Death*	1 (1.2)	1 (1.4)	2 (1.9)

*Deaths were due to PD and unknown and each not deemed related to study drug.
Note: population is based on enrolled patients; one patient did not receive study drug

References: [1]Villalona-Calero, M., et al., (2023). Mol Cancer Ther. DOI: 10.1158/1535-7163.TARG-23-B159; [2]Richters, A., et al., (2021). Cell Chem. Biol. DOI: 10.1016/j.chembiol.2020.10.001; [3]Freeman, D. B., et al., (2023). J Med Chem. DOI: 10.1021/acs.jmedchem.3c01233; [4]Data Resources Group (2022). Data on file; [5]Huang, C. H., et al., (2014). Genes & Dev. DOI: 10.1101/gad.244368.114; [6]Gage, M. M., et al., (2019). Oncotarget. DOI: 10.18632/oncotarget.26809; [7]Togashi, Y., et al., (2018). Modern Pathology. DOI: 10.1038/s41379-018-0008-8;

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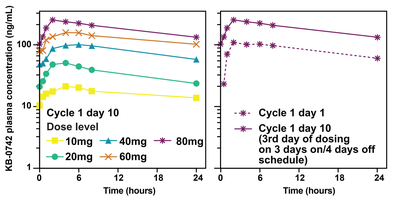
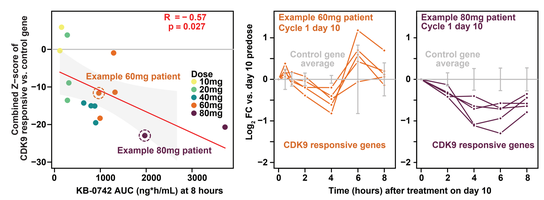
KB-0742 achieved plasma concentrations leading to demonstratable on-target pharmacodynamic activity in peripheral blood mononuclear cells (PBMCs) and tumor cells

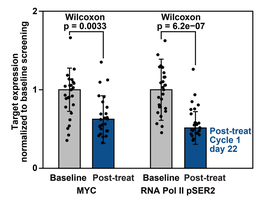
KB-0742 continues to show dose linear PK up to 80mg 3 day on/4 day off with a long plasma half-life of 24hrs



Deeper and more sustained downregulation of CDK9-dependent genes in PBMCs observed at 80mg 3 days on/4 days off dose cohort

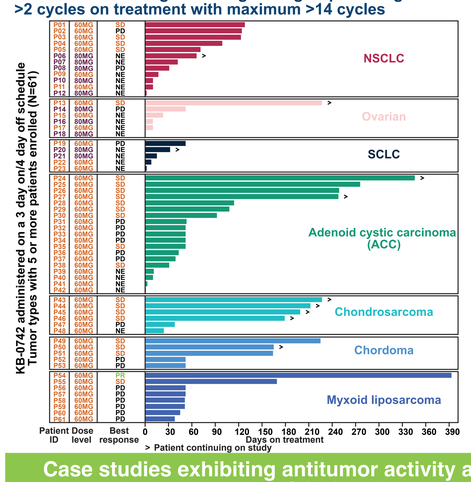


Reduction in MYC and pSER2 observed in tumors after 1st cycle

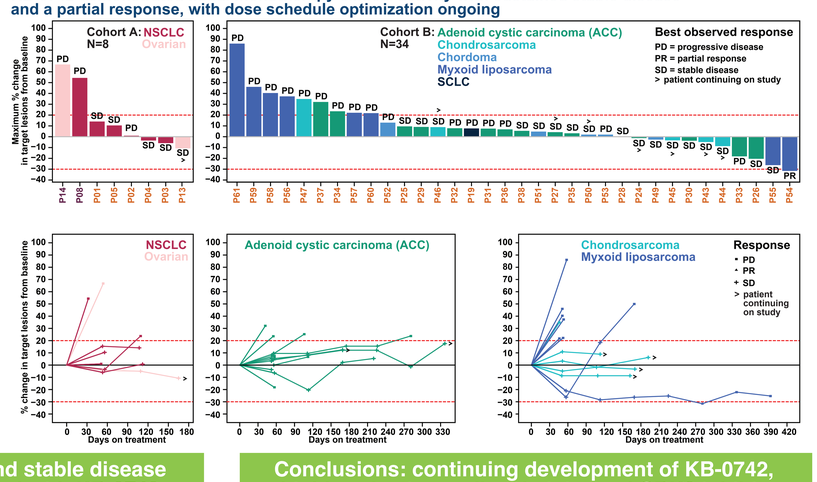


KB-0742 monotherapy demonstrates clinical activity with durable stable disease in heavily pretreated patients with transcriptionally addicted tumors

Patients in the 60mg and 80mg dose groups averaged >2 cycles on treatment with maximum >14 cycles



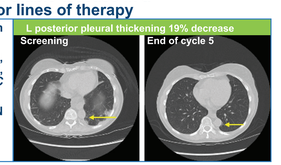
KB-0742 demonstrated initial monotherapy clinical activity with sustained stable disease and a partial response, with dose schedule optimization ongoing



Case studies exhibiting antitumor activity and stable disease in ovarian cancer and NSCLC patients treated with KB-0742

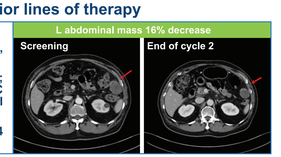
Ovarian cancer: Target lesion reduction and longterm stable disease in a MYCL1+ platinum refractory patient with multiple prior lines of therapy

- 75-year-old female Stage 3b high-grade serous ovarian cancer in September 2022
- Foundation Tissue: PIK3CA, SOX2, TP53, EWSR, *FGF12* amplified, KDM5A, *MYCL1* amplified, *PRKC1* amplified, *TERC* amplified, MSS, TMB2. Invitae: negative for BRCA1/2, ATM, MSH6+; Tempus: *MYC* amplified (4+ copies) and overexpressed (cMYC H score > 50)
- Prior lines: Paclitaxel+ Carboplatin, Pembrolizumab: (OCT 22- JAN 23); DS-6000A (FEB 23-JUN 23; SD = best response)
- KB-0742 treatment: On study drug through C10 at 60mg 3 days on/4 days off and ongoing; SD at C2 for 196 days+



NSCLC: Target lesion reduction in a patient with 5 prior lines of therapy

- 70-year-old male Stage 3 NSCLC dx 2018, now Stage 4
- Guardant 360: BRAF V600E, TP53 C176Y, TP53 R273H, SMO P736P, NTRK3 S433S
- 5 prior lines of therapy: Carboplatin/Pemetrexed (FEB 18- APR 18); Dabrafinib/Trametinib (FEB 19-20); Pembrolizumab (MAY 20-DEC 21); Pemetrexed (JAN 22-UNK 23, PD best response); Docetaxel (JUN 23-JUL23, PD best response)
- KB-0742 treatment: On study drug through C5 at 60mg 3 days on/4 days off before discontinuation; SD at C2 for 71 days



Conclusions: continuing development of KB-0742, a highly selective orally administered CDK9 inhibitor

- KB-0742 continues to demonstrate a manageable safety and tolerability profile as it has progressed through dose escalation.
- At the 60mg dose, MYC reductions were observed in paired biopsy tumor tissues. There was a deepening reduction of CDK9 sensitive transcripts in PBMCs seen at the 80mg dose compared to the 60mg dose.
- Based on these data, the continued patient benefit observed, the internal pharmacokinetic modeling data showing a greater than ten-fold increase in time above a preclinically determined efficacy threshold, we expect to see increased efficacy in the 80mg 4 days on/3 days off expansion cohort expected to begin enrolling in the third quarter of 2024.

80mg 4 days on/3 days off schedule increases time above threshold